Growth Factors and the Mesangium

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ABSTRACT

Growth factors are prime candidates to mediate and modulate the functions of the mesangium. Mesangial cells are effector cells producing a number of growth factors that act in an autocrine manner to regulate their own function. Mesangial cells are also targets for growth factors released from neighboring glomerular cells or infiltrating cells and platelets. Growth factors may promote hypertrophy, proliferation, matrix metabolism, and immune-inflammatory and vasoactive properties of mesangial cells. These peptides represent important mediators of mesangial cell responses to injury. Platelet-derived growth factor mediates predominantly cell proliferation, whereas transforming growth factor beta mediates mesangial cell matrix expansion. Mesangial cells may also modulate some of the hemodynamic effects of growth factors, such as the increased renal vascular resistance in response to platelet-derived growth factor and epidermal growth factor or the increased RBF and GFR in response to insulin-like growth factor-1. Changes in the expression of growth factors or their receptors during the course of glomerular injury point to a potential role in mediating some of the pathologic changes in vivo. Several agents appear to antagonize the mitogenic and perhaps other effects of growth factors in mesangial cells. Such agents include adenylate cyclase as well as guanylate cyclase agonists. Recent studies also suggest that some traditional vasoactive agents may activate metabolic processes in mesangial cells similar to peptide growth factors. Collectively, these studies point to the interaction of both hemodynamic and metabolic factors in the response and contribution of glomerular and specifically mesangial cells to injury.

Key Words: Platelet-derived growth factor, epidermal growth factor, insulin-like growth factor, transforming growth factor-beta, proliferation, glomerulonephritis

The glomerulus is invariably involved in the course of many types of immune- or nonimmune-mediated kidney disease [1,2]. The involvement of the glomerulus manifests itself (Table 1) as (1) hypercellularity due to intrinsic cell proliferation and/or proliferation of infiltrating inflammatory cells; (2) subtle morphologic evidence of injury to one of the glomerular cell types; (3) glomerular hypertrophy with or without hypertrophy or proliferation of cells such as mesangial cells; (4) changes in basement membrane and matrix including expansion and sclerosis; and (5) functional changes, which may include a decrease or increase in glomerular blood flow, filtration rate, and hydrostatic pressure. Glomerular pathology results from primary glomerular disease or may be secondary to an interstitial process that results in a significant loss of renal mass. Mesangial cells participate in the structural and functional changes that accompany glomerular pathology as targets as well as effector cells that may modify the outcome of glomerular injury [3–5]. When one considers the biologic effects of growth factors (Table 2), their potential involvement in glomerular and specifically mesangial cell pathology becomes clear [6,7]. These peptides participate in such diverse processes as growth, whether it is hypertrophy or proliferation, the regulation of matrix synthesis and degradation, development and differentiation, immunoinflammatory responses, and, importantly, the regulation of vascular tone.

SOURCES AND ACTIONS OF GROWTH FACTORS

What are the sources of these peptides that interact with glomerular cells? Although the systemic circulation is a potential source for some of these peptides, such as epidermal growth factor (EGF) and insulin-like growth factor 1 (IGF-1), mounting evidence suggests that these peptides do not primarily function in an endocrine manner, but rather in an autocrine or short-term paracrine fashion. An important source of peptide growth factors in the glomerulus are intrinsic glomerular cells as well as infiltrating inflammatory cells and platelets (Table 3). Activated platelets, monocytes, tissue macrophages, and lympho-
TABLE 1. Pathology of the glomerulus

Hypercellularity
Cell Injury
Hypertrophy
Matrix Expansion and Sclerosis
Increased Capillary Permeability
Hemodynamic Abnormalities

TABLE 2. Biologic effects of growth factors

Growth: Hypertrophy and Proliferation
Matrix Synthesis and Degradation
Vascular Tone
Immune-Inflammatory Responses
Development and Differentiation

TABLE 3. Sources of growth factors in the glomerulus

<table>
<thead>
<tr>
<th>Source</th>
<th>Growth Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial Cells</td>
<td>PDGF, IL-1, IGF-1, TNF-α, TGF-β, IL-6, M-CSF, GM-CSF, IL-8</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>PDGF, TGF-β</td>
</tr>
<tr>
<td>Epithelial Cells</td>
<td>Heparin, TGF-β?</td>
</tr>
<tr>
<td>Infiltrating Cells</td>
<td>Monocytes ~ macrophages (IL-1, PDGF, TNF-α, IGF-1)</td>
</tr>
<tr>
<td></td>
<td>Platelets (PDGF, EGF, TGF-β, PF-4)</td>
</tr>
<tr>
<td></td>
<td>Lymphocytes (TGF-β, TNF-β)</td>
</tr>
</tbody>
</table>

* TNF, tumor necrosis factor; M-CSF, macrophage colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

cytes infiltrating the glomerulus in the course of many glomerular diseases could release substantial amounts of these peptides (8–11). In vivo studies involving the depletion of these inflammatory cells support their critical role in mediating glomerular pathology (9–11). Intrinsically glomerular cells, particularly mesangial cells, under in vitro culture conditions are an additional and likely important source (12–17). Mesangial cells synthesize several peptide growth factors and cytokines such as interleukin-1 (IL-1), platelet-derived growth factor (PDGF), IGF-1, and macrophage and granulocyte-macrophage colony-stimulating factors (Table 3), as well as a number of other interleukins and monocyte chemotactic peptides. Mesangial cells express mRNA that encode for several growth factors as well as growth factor-binding proteins (7,16,17). Some of these binding proteins regulate the activity of the secreted growth factor. Human, mouse, and rat mesangial cells secrete PDGF, express PDGF A- and B-chain mRNA, and proliferate in response to PDGF (14,17). The abundant PDGF A-chain mRNA and results of radioreceptor assay suggest that the PDGF AA homodimer represents the major PDGF isoform secreted by mesangial cells. Mesangial cells, however, predominantly express PDGF-β receptor subunits. Our studies in cultured mesangial cells suggest that the PDGF-α receptor subunit is down-regulated by endogenous PDGF. In addition to its mitogenic effect, PDGF is a potent chemoattractant for mesangial cells and stimulates contraction of the cells (4,18). In addition to PDGF, mesangial cells from all three species also secrete IGF-1 activity as well as IGF-1 binding proteins. IGF-1 also stimulates DNA synthesis in mesangial cells (7,16). Perhaps the best-characterized effect of these compounds on mesangial cells is their mitogenic effect (Table 4). In our studies, primarily in human mesangial cells, we find that PDGF and thrombin are the most potent mitogens for mesangial cells, followed by fibroblast growth factor, EGF, and transforming growth factor alpha (TGF-α) (8). Most mesangial cell mitogens induce PDGF A- and B-chain mRNA in a coordinate fashion, suggesting a central role for PDGF genes and their secreted products in mediating the mitogenic effect. Some peptides inhibit mesangial cell proliferation. Prominent among these is transforming growth factor beta (TGF-β) (8,19). In addition, cAMP and cGMP, as well as agents that increase the cellular accumulation of these nucleotides, are potent inhibitors of mesangial cell proliferation. Also of interest are the recent observations that several agents such as endothelium-derived relaxing factor and calcium channel antagonists inhibit mesangial cell growth (3,7). The mechanisms by which these factors inhibit cell growth are not clear. Endothelium-derived relaxing factor may act by increasing cGMP levels similar to atrial natriuretic factor. Mesangial cell growth is also modulated by normal and abnormal matrix (7,20). Proliferating glomerular cells may contribute not only to morphologic but also functional abnormalities of the glomerulus. There are several potential mechanisms by which glomerular cell proliferation and specifically mesangial cell proliferation affect glomerular function. For example, proliferating cells may undergo phenotypic modulation, which results in enhanced matrix pro-

TABLE 4. Effect of growth factors on mesangial cells

<table>
<thead>
<tr>
<th>Factor</th>
<th>Proliferation</th>
<th>Matrix Synthesis</th>
<th>Migration</th>
<th>Contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGF</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>EGF</td>
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<tr>
<td>TGF-β</td>
<td>↓</td>
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<td>↑</td>
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<tr>
<td>IGF-1</td>
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<tr>
<td>bFGF</td>
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</tbody>
</table>

* FGF, fibroblast growth factor.
duction and secretion, changes in growth factor expression, and up- or down-regulation of receptors for growth factors, cytokines, or vasoactive hormones. Finally, simple mechanical clogging of the glomerular capillaries may also result from overgrowth of these cells. An intriguing possibility is that the dysregulated growth of glomerular cells may lead to or at least contribute to the progression of glomerular disease, as suggested by observations in transgenic mice (21,22).

In human mesangial cells, IGF-1 appears to be a more potent stimulus of protein and collagen synthesis than TGF-β; under the same conditions, PDGF had no effect on collagen synthesis (H.E. Abboud et al. unpublished observation). These in vitro studies suggest that although the major biologic effect of PDGF is to promote hypercellularity, IGF-1 and TGF-β promote matrix expansion. In vitro events, however, may be different from these in vitro observations. Because PDGF stimulates the release of latent TGF-β, which is likely to be activated by proteolytic enzymes at sites of inflammation, PDGF may contribute indirectly to matrix metabolism in vivo.

ROLE OF GROWTH FACTORS IN VIVO

Several in vitro studies suggest that peptide growth factors may be involved as mediators of glomerular pathology. The potential involvement of PDGF in proliferative glomerular diseases is suggested by the increased expression of this protein in a number of proliferative glomerular diseases in humans and experimental animals (23–29). Of interest is the recent observation that the PDGF-β receptor is also up-regulated in proliferative glomerular diseases as well as in transplant rejection (23). Gesualdo et al. (28) reported increased expression of PDGF and PDGF B-chain mRNA in kidneys of mice with immunoglobulin A nephropathy. PDGF localized in mesangial areas and to a lesser extent in extraglomerular structures. Increased expression of PDGF was also demonstrated by immunohistochemical techniques in glomeruli from biopsies of patients with proliferative glomerular diseases. Iida and his colleagues (27) also recently reported that PDGF may be an important factor in the pathogenesis of mesangial proliferative nephritis. These authors found increased expression of PDGF and PDGF receptors as well as their respective mRNA in glomeruli in a rat model of mesangial proliferative nephritis induced with an antibody to Thy-1 antigen present on mesangial cells. More recent in situ hybridization studies also localized PDGF mRNA to glomerular cells (29). These studies do not establish a role for PDGF as the cause of the proliferative process. Studies with receptor antagonists or antibodies to PDGF should provide more definitive answers. TGF-β is another peptide that appears to be involved in mediating glomerular pathology. TGF-β binds to isolated mouse glomeruli as well as to glomerular epithelial, mesangial, and endothelial cells. Jaffer et al. (8) and MacKay et al. (19) demonstrated an inhibitory effect of TGF-β on all glomerular cell types. TGF-β also stimulates fibronectin synthesis in glomerular epithelial and mesangial cells. A potential role of TGF-β in mediating matrix expansion in proliferative glomerular disease has recently been demonstrated by Border et al. (24,25). These investigators demonstrated an increased production and activity of TGF-β1 in isolated glomeruli of rats with a proliferative glomerular disease induced by the injection of anti-Thy-1 antibody. Most recently, these investigators demonstrated that the administration of anti-TGF-β1 at the time of the induction of glomerular disease suppresses the increased production of the extracellular matrix and dramatically attenuates the histological manifestation of the disease (25). TGF-β1 is a potent stimulus of proteoglycan synthesis in cultured mesangial cells as well as of fibronectin and other matrix molecules in cultured glomerular epithelial cells.

Renal and, specifically, glomerular hypertrophy has been incriminated as a risk factor for the progression of renal disease (26). Some investigators also suggest that hypertension is a prerequisite for mesangial expansion and eventual sclerosis of that glomerular microvascular bed (21,22). Peptide growth factors may also be involved in glomerular hypertrophy, as has been suggested for IGF-1. Recent studies with mice transgenic for growth hormone (GH), growth hormone-releasing factor (GHRF), and IGF-1 demonstrated that only mice transgenic for GH and GHRF develop hypertrophy and sclerosis. Mice transgenic for IGF-1 did develop some hypertrophy but little sclerosis (21,22). This occurred even when circulating levels of IGF-1 in the animals transgenic for IGF-1 were higher than those transgenic for GH and GHRF. It should be emphasized, however, the glomerular levels of IGF-1 were not reported, and a local increase of IGF-1 may be responsible for the hypertrophy. Alternatively, additional growth factors other than IGF-1 may mediate the effect of GH. Of interest in these studies is the disproportionate hypertrophy of glomeruli compared with total kidney or total body weight of the animals. A potentially interesting role for IGF-1 in mediating the increased RBF and GFR in remnant nephrons is suggested by studies showing that the infusion of IGF-1 in fasting rats increases RBF and GFR (30). Additional evidence suggests that IGF-1 may be involved in the pathogenesis of diabetic nephropathy (31). Mesangial cells from genetically diabetic mice (db/db) express higher levels of IGF-1 receptors compared with mesangial cells from control db/m mice. IGF-1 and insulin receptor mRNA expression were increased in db/db cells grown in the pres-
ence of high-glucose medium. Abnormalities in IGF-1 receptor regulation in this as well as in other models of glomerular injury should be explored. A role for other growth factors in mediating glomerular or mesangial hypertrophy needs to be explored. The increased expression of the PDGF A chain during myometrial hypertrophy may be a clue to the functions of the PDGF A chain in the mesangium (32).

EGF is another potential candidate that may mediate hypercellularity and perhaps matrix expansion in the glomerulus (33). Specific receptors for EGF are present in mesangial cells. EGF is also a potent mitogen for mesangial cells. EGF also contracts mesangial cells and, when infused into the aorta, decreases RBF and GFR (33). Some of the effects of EGF are likely mediated by cyclooxygenase metabolites.

IL-6 is another cytokine that may mediate proliferative glomerular diseases (34,35). Mice transgenic for IL-6 have been shown to develop in addition to plasmacytosis, a proliferative mesangial lesion. In addition, changes in the receptor expression in mesangial cells are also encouraging. These observations, taken together with the evidence from extrarenal tissue, provide an excellent rationale to explore the role of growth factors as mediators of glomerular pathology. Detailed chronicologic studies of the cellular interactions, growth factor expression, and hemodynamic changes at each stage of glomerular injury are needed. Such studies will permit understanding the nature of the cellular interactions and will identify the predominant expression of certain growth factors that precede the development of each phase of the glomerular lesion. Delineating a precise source and role of growth factors in mediating pathologic changes is an area of fruitful investigation. The prospects of developing receptor antagonists or specific antibodies to some of these peptides will provide a more rational approach to interrupt glomerular injury.

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